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Therapeutic efficacy of antisense oligonucleotides in mouse models of CLN3 Batten disease

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Abstract

CLN3 Batten disease is an autosomal recessive, neurodegenerative, lysosomal storage disease caused by mutations in *CLN3*, which encodes a lysosomal membrane protein. There are no disease-modifying treatments for this disease that affects up to 1 in 25,000 births, has an onset of symptoms in early childhood and typically is fatal by 20–30 years of life. Most patients with CLN3 Batten have a deletion encompassing exons 7 and 8 ($CLN3^{\Delta ex7/8}$), creating a reading frameshift. Here we demonstrate that mice with this deletion can be effectively treated using an antisense oligonucleotide (ASO) that induces exon skipping to restore the open reading frame. A single treatment of neonatal mice with an exon 5-targeted ASO-induced robust exon skipping for more than a year, improved motor coordination, reduced histopathology in $Cln3^{\Delta ex7/8}$ mice and increased survival in a new mouse model of the disease. ASOs also induced exon skipping in cell lines derived from patients with CLN3 Batten disease. Our findings demonstrate the utility of ASO-based reading-frame correction as an approach to treat CLN3 Batten disease and broaden the therapeutic landscape for ASOs in the treatment of other diseases using a similar strategy.